REMARKS

Claims 13-18, 20-22, 28, and 32-40 are now pending in this application. Claims 19, 30, and 31 are cancelled in this amendment (claims 1-12, 23-27, and 29 were canceled previously) and claims 36-40 are added. Claims 13, 15, 20, 22, and 28 have been amended. **Claim 13** was amended to correct a grammatical error; **claim 15** was amended to remove the reference to SIV (which was superfluous, as it failed to further limit the claim); **claim 20** was amended to specify that the full-length surface envelope protein is gp120-SU of HIV-1 and to specify that the truncated variant of the transmembrane envelope protein results from a stop codon at position 712 (see the specification at, for example, at page 4, lines 25-27, and at page 8, lines 20-22); and **claim 28** was amended to specify that the vector mediates the transfer of a foreign gene into a CD4-positive cell of a mammal. No new matter has been added.

The Invention

The invention relates to retroviral vectors that include a viral core of a murine leukemia virus (MLV) and a viral envelope protein that includes a full-length surface envelope protein and a truncated transmembrane envelope protein from a human immunodeficiency virus (HIV) or a simian immunodeficiency virus (SIV). These retroviral vectors can be used, for example, to transfer genes into selected cell types, such as CD4-positive mammalian cells. The invention also encompasses methods of preparing packaging cells.

35 U.S.C. § 112, ¶ 1

Claims 19 and 20 are rejected as allegedly lacking enablement (Office Action at pages 5-6).

As Applicants have cancelled claim 19 (without prejudice to future rights), this ground for rejection is now moot and, therefore, should be withdrawn.

With respect to claim 20, Applicants have replaced the claim term "pLβAc/env-Tr712-neo" with the phrase, "a nucleic acid sequence encoding the full-length surface envelope protein gp120-SU of HIV-1 and the truncated variant of the transmembrane envelope protein resulting from a stop codon at position 712." Thus, the vector now claimed does not require the "specific

cell line and plasmids" referred to by the Examiner (Office Action at page 6, lines 5-6). Accordingly, this ground for rejection should be withdrawn.

Claims 30 and 31 are also rejected as allegedly lacking enablement (Office Action at pages 7-9). As Applicants have cancelled claims 30 and 31 (without prejudice to future rights), this ground for rejection is also moot and should be withdrawn.

35 U.S.C. § 103(a)

Claims 13-22, 28, and 32-35 are rejected as allegedly being obvious over Denesvre *et al.* (*J. Virol.*, 70:4380-4386, 1996; herein, "Densevre") in view of Salmons *et al.* (*Leukemia*, 9(Suppl.):S53-S60, 1995; herein, "Salmons"), Wilk *et al.* (*Virology*, 189:167-177, 1992; herein, "Wilk"), and Zingler *et al.* (*J. Virol.*, 67:2824-2831, 1993; herein, "Zingler") (Office Action at page 10). Applicants respectfully traverse this rejection.

The Examiner states that the rejection stands "for the reasons set forth in the Office Action of December 6, 2000" (Office action at page 10) and, in addition, addresses Applicants' most recent remarks (Office action at pages 11-12). To help place the further remarks below in context, Applicants summarize the Examiner's argument as follows (this is a faithful attempt to reproduce the Examiner's remarks at pages 11-12 of the Office action without reproducing them in their entirety):

* The conclusion drawn in the prior Office action is not the Examiner's alone; the simple rule relied upon in Denesvre (discussed further below) is specifically set forth by Denesvre based on the data and scientific reasoning presented in their reference.

* Denesvre's rule applies to the claimed subject matter because Denesvre explicitly discusses the problem of HIV-1 Env containing a long cytoplasmic tail that cannot be incorporated into MuLV particles.

* The test is what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art

* Salmons teaches and provides examples of pseudotype virions and suggests making MLV/HIV-1 pseudotypes.

* Obviousness does not require absolute predictability of success; for obviousness, all that is required is a reasonable expectation of success.

* The reduction to practice of several examples provides clear evidence that various combinations (of viral cores and viral envelopes) were successful.

In reply, Applicants address these points (roughly in order).

Denesvre and the "simple rule": Denesvre studied only "complete, truncated, or chimeric Friend murine leukemia virus (F-MuLV) and human T-cell leukemia virus type 1 (HTLV-1) envelopes" (Denesvre *et al.*, page 4380, abstract); none of the studies employed a retroviral vector comprising an MLV core and a virus envelope comprising a HIV or SIV envelope, as Applicants now claim. Moreover, and despite Denesvre's discussion of HIV, there is no actual suggestion that one should make such a pseudotype or that doing so would produce a successful retroviral vector. Denesvre's statements regarding HIV are based on prior observations that "HIV-1 Env containing a long cytoplasmic tail is not incorporated into MuLV particles" (page 4385, column 1). Based (presumably) on that observation, together with the studies conducted, Denesvre *suggested* "the simple rule that retroviral cores allow incorporation of heterologous envelopes whose cytoplasmic tails are smaller than that of the original parental envelope" (page 4385, column 1). That suggestion, however, falls short of suggesting that one should make the particular retroviral vector now claimed. As the "rule" is put forth as a general rule, it also falls short of providing a reasonable expectation that such a vector would be capable of effectively targeting CD4-positive cells. This is not to say that Denesvre is not significant; it may well represent an extremely important contribution to the field. That does not mean, however, that Denesvre's suggested rule (or any other part of the disclosure) satisfies the legal standard for obviousness. Denesvre (alone or in combination with the other cited references) may encourage those of ordinary skill in the art to experiment, but that is not sufficient for a *prima facie* case of obviousness. Rendering a vector obvious-to-try is simply not enough.

The subject matter taken as a whole: Applicants agree that the references cited must be considered as a whole. However, each reference must be examined and sufficient motivation and the required expectation for success must be found – whether in a given reference or in the

references combined. The Examiner relies on Salmons as providing "clear and specific motivation" due to the suggestion that one *could* make MLV/HIV-1 pseudotypes (*see* Salmons at page S58, column 1). Salmons, however, suggests that one *could* take a number of different approaches to generate effective retroviral vectors. Salmons is a review article that describes various strategies, including those that (Abstract; emphasis added):

> (1) limit therapeutic gene delivery, using pseudotyping *or* vectors based on retroviruses that show a restricted infection spectrum *or* (2) limit the expression of transferred genes by inclusion of tissue specific promoters *or* cis acting regulatory elements.

Salmons concludes as follows (S58, column 2; emphasis added):

> In conclusion, *a synthesis of* the different approaches outlined above should provide a strong framework for the construction of safe, tissue targeted RVs [retroviruses] for future *in vivo* gene therapy.

One of ordinary skill in the art would take Salmons for all that it discloses; as a whole, it is a review of various possibilities, with no actual suggestion as to which (or which "synthesis" or combination of possibilities) one should try.

Moreover, and with all due respect, Applicants contend that the Examiner has impermissibly used hindsight reconstruction in making this rejection, at least insofar as Salmons is concerned. Where, except in Applicants' specification, is the suggestion that pseudotyping should be carried out? Why should one select pseudotyping rather than infection spectrum-limited vectors or tissue-specific promoters or other regulatory elements, all of which, and combinations of which, Salmons also suggests?

Predictability: Applicants also recognize that the prior art must provide only a reasonable expectation for success. The Examiner is correct in that absolute predictability is not required. Even so, the requirement is not met in the present case. The prior art uses various assays to demonstrate that, for example, MuLV/HTLV-1 pseudotypes have promising characteristics (*e.g.*, they confer virion infectivity), but there is no demonstration that the MLV/HIV (or MLV/SIV) retroviral vectors now claimed would exhibit those (or other desirable) characteristics. Nor does the art explain why one would reasonably expect pseudotypes bearing

HIV or SIV envelope proteins to effectively target CD4-positive cells. The number of pseudotypes that have been examined is irrelevant. For obviousness, there must be a reason why the results obtained with distinct pseudotypes would predict success with the retroviral vector now claimed. There must be a reasonable expectation of success *for the composition claimed.*

In light of the foregoing remarks, Applicants respectfully request that these grounds for rejection be withdrawn. *Should the Examiner decide to maintain the rejection on the basis of obviousness, Applicants request that they be granted a telephonic interview at the Examiner's first convenience.* Applicants thank the Examiner in advance for this courtesy.

Enclosed is a $950 check for the Petition for Three-Month Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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